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A Patient With Interstitial Deletion of the Short Arm of Chromosome 3 (pter→p21.2::p12→qter) and a CHARGE-Like Phenotype

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We report on a 4-month-old boy with a de novo interstitial deletion of the short arm of chromosome 3 (pter → p21.2::p12 → qter) and clinical findings typical of proximal 3p deletion together with coloboma of iris, heart defect, choanal atresia, retardation of growth and development, genital hypoplasia, and ear anomalies. Family history was unremarkable and parental chromosomes were normal. The clinical manifestations of the patient are compared with those of 10 patients previously described with a proximal 3p deletion. The additional CHARGE-like phenotype is discussed. Am. J. Med. Genet. 69:413–417, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: chromosome 3p; interstitial deletion; CHARGE syndrome; multiple congenital anomalies

INTRODUCTION

Interstitial deletion of the proximal short arm of chromosome 3 is rare. To our knowledge, only 10 patients with this chromosomal rearrangement and different breakpoints have been reported [Crispino et al., 1995; Hertz et al., 1988; Karimi-Nejad et al., 1990; Kogame & Kudo, 1979; Mitter et al., 1984; Naritomi et al., 1988; Neri et al., 1984; Sichong et al., 1981; Wyandt et al., 1980], none with the same breakpoints as in our patient. We report on a boy with an interstitial deletion of the short arm of chromosome 3 [46,XY,–3, +del 3(pter→p21.2::p12→qter)] who died at the age of 4 months. In addition to the typical clinical findings of an interstitial deletion of 3p, a CHARGE-like phenotype was noted.

CLINICAL REPORT

The propositus was the first child of a healthy, nonconsanguineous couple of German origin, a 36-year-old mother and a 42-year-old father. The boy was found dead in bed one morning, in the absence of any warning symptoms, at the age of 4 months. We examined the patient in the Department of Forensic Medicine, University of Essen, for diagnostic evaluation after autopsy because of congenital anomalies.

The family history was unremarkable. The pregnancy was uneventful, routine investigations were declined by the parents. He was born after 39 weeks of gestation. Birth weight was 2,320 g (–1.2 SD), length 46 cm (–1.6 SD), and head circumference 32 cm (–2.6 SD). Apgar scores were not reported. Profound respiratory distress and cyanosis required intubation and

Fig. 1. Patient's face at the age of nine weeks showing broad forehead with low frontal hairline, short, broad based nose with anteverted nostrils, and low-set, abnormal left ear

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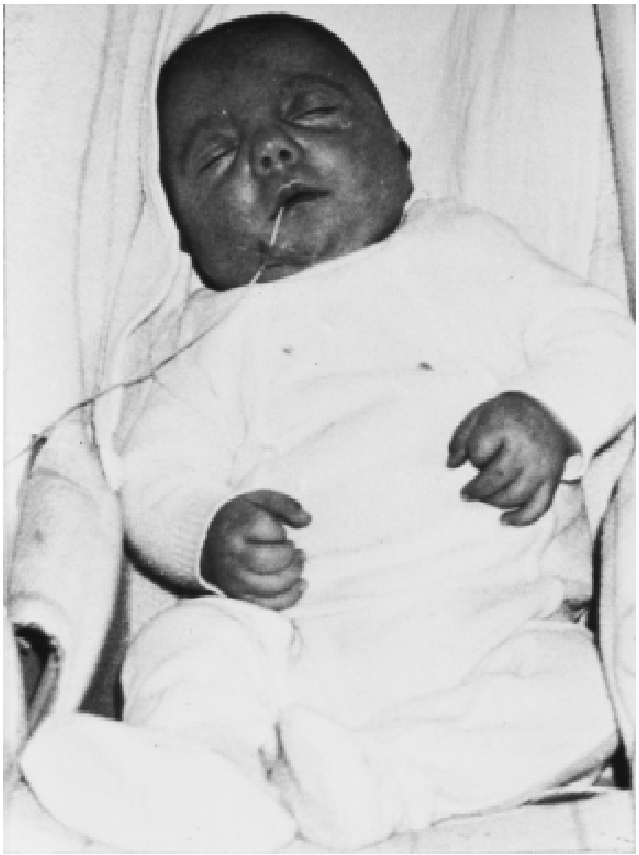


Fig. 2. Propositus at the age of four months showing the abnormal positioning of fingers on both sides.

mechanical ventilation. Seizures started on the first day of life and were treated with phenobarbital. Right choanal atresia was noted. Poor and uncoordinated sucking required tube feeding. Ocular examination showed bilateral coloboma of iris and normal fundi. Ultrasonographic investigation of the heart showed an atrial and ventricular septal defect, and mild pulmonary stenosis. His psychomotor development was retarded. Extension at the knees was diminished and the muscle tone was strongly increased.

At the time of his death at the age 4 months, his weight was 4,550 g (–3.1 SD), length 52 cm (–5.1 SD), and head circumference 35 cm (–6.2 SD). We noted a broad forehead, a low frontal hairline, hypertelorism, a short, broad based nose with anteverted nares, bilateral microphthalmia and coloboma of the iris, full cheeks, micrognathia, a short philtrum (Fig. 1), high and vaulted palate, small, low-set ears with hypoplasia of the upper portion of the helix. Finger positioning showed camptodactyly of the second finger with the third and fourth finger overlapping the index finger (Fig. 2). His hands were positioned in ulnar deviation and transverse creases were found in both palms. He had pes planus congenitus, sandal gaps bilaterally, sacral dimple and hypoplastic scrotum, micropenis and cryptorchidism.

The autopsy demonstrated an asymmetric occipital skull, absence of gallbladder, abdominal testes, and stenosis and sclerosis of the intrapulmonary pulmonary arteries. The patient's death was ruled as due to bronchopneumonia. Macroscopic investigation of the brain showed micropolygyria, fronto-central schizogyria and microcystic lesions in the district of the arteria cerebri media bilaterally. The corpus callosum was severely hypoplastic and the septum pellucidum was aplastic. The adhesio interthalamica was absent. Histologic examination showed hypoplastic white brain matter.

CYTOGENETIC FINDINGS

Chromosome analysis was carried out on cultured skin fibroblasts and blood lymphocytes in the propositus, and from both parents on blood lymphocytes. Analysis of the postmortem fibroblast cultures at 390 G-band-level showed an interstitial deletion of bands p21.2 to p12 in the proximal short arm of chromosome

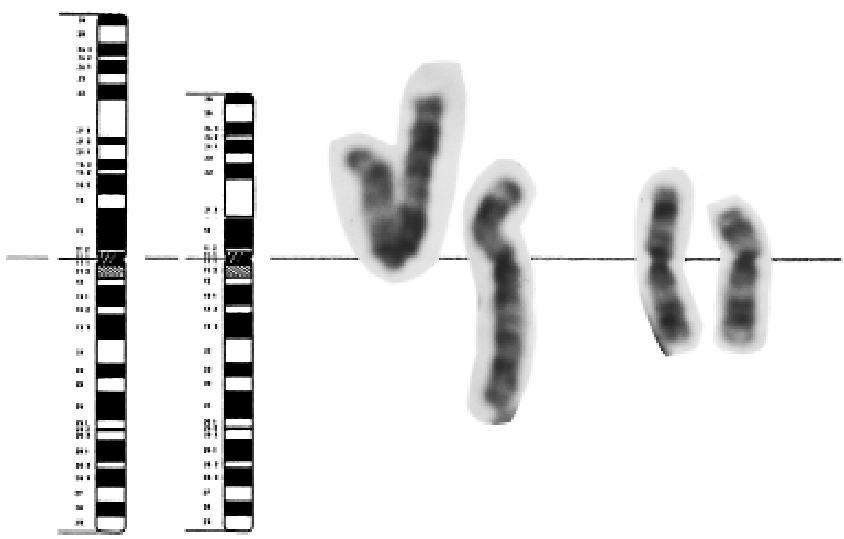
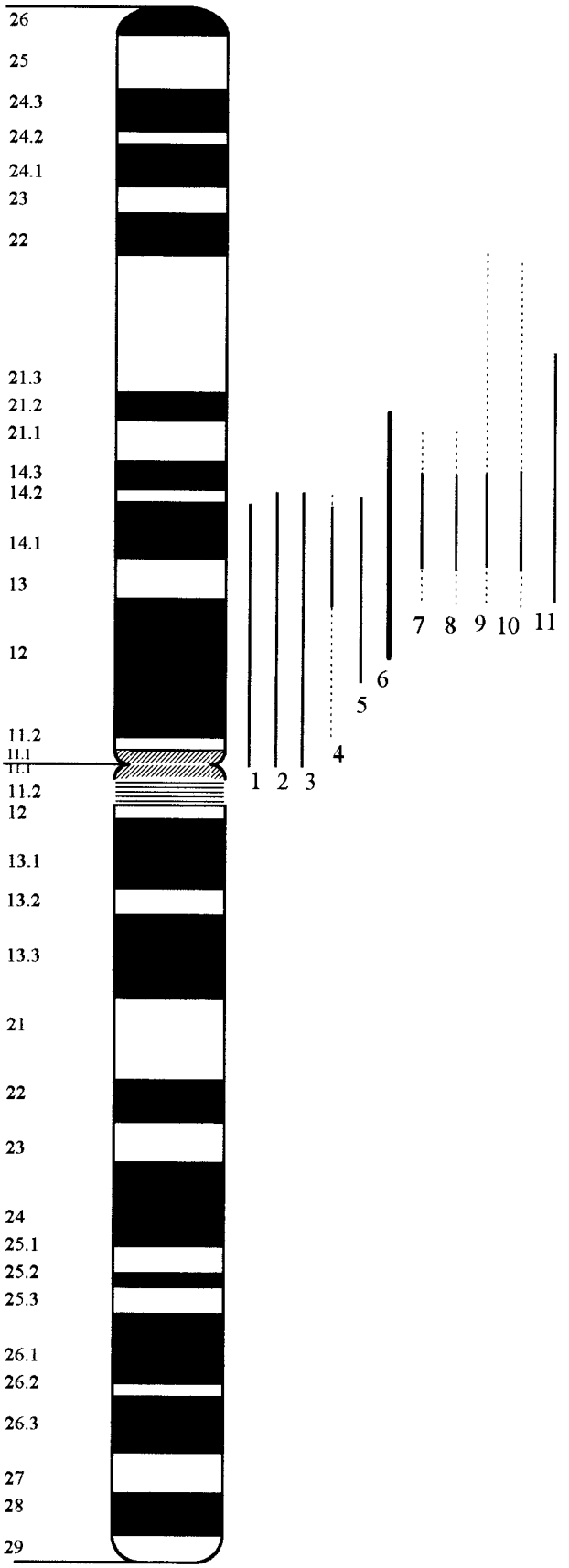


Fig. 3. Chromosomes 3. Normal chromosome on left, abnormal chromosome on right; the interstitial deletion extends from 3p12–3p21.2.



3, resulting in the following karyotype: 46, XY, –3, + del 3 (pter → p21.2::p12 → qter) (Fig. 3). The same karyotype was also found in lymphocytes in an external private laboratory. Both parents had normal chromosomes.

DISCUSSION

With the addition of this report, a total of 11 cases of proximal interstitial deletion of the short arm of chromosome 3 have been published. In addition, there are some cases with deletions of the short arm of chromosome 3 which involve the terminal segment from 3p23 or 3p24. These cases are not discussed here.

In 1984, Neri et al. suggested a proximal 3p deletion phenotype including 4 major manifestations, the first being a characteristic facial appearance. Our patient had overlapping breakpoints (Fig. 4) and strikingly similar facial findings in comparison to the previously described patients with proximal breakpoints in 3p11 or 3p12 [Sichong et al., 1981; Hertz et al., 1988; Neri et al., 1984, Naritomi et al., 1988]. The facial phenotype is characterized by a low forehead, epicanthic folds, hypertelorism, broad nasal bridge, short, stubby nose with anteverted nares, short philtrum, small mouth, micrognathia, and low-set and "dysplastic" ears. Thus, in comparison to the patients of the literature with proximal 3p interstitial deletion our patient confirms the hypothesis of a recognizable facial phenotype. In 3 of the 5 reports [Karimi-Nejad et al., 1990; Mitter et al., 1984; Short et al., 1986] with the proximal breakpoint in 3p13 no photo of the described patient is included in the paper. However, the patients of Kogame and Kudo [1979] and Wyandt et al. [1980] are illustrated, but show a different facial phenotype.

Neri et al. [1984] suggested that the other 3 major manifestations of the proximal 3p deletion phenotype are limitations of joint movements, deformities, including ulnar deviation of hands, camptodactyly, and calcaneovalgus feet, and delayed psychomotor development. These findings were also present in our patient, although they were not described in all patients with a more telomeric interstitial deletion 3p (Table I).

Other reported anomalies, such as heart defects and intestinal malformations, including agenesis of gall bladder, posteriorly placed anus, and Meckel diverticulum, seem to be nonspecific, being also present in other chromosomal rearrangements, thus, do not help in defining the proximal interstitial deletion of 3p phenotype. In addition to the clinical manifestations mentioned above, which fit into the spectrum of an interstitial deletion of 3p, our patient had (1) bilateral coloboma of iris, (2) atrial and ventricular septal defect, mild pulmonic stenosis, (3) atresia of the right choana, (4) growth retardation, (5) delayed psychomotor devel-

Fig. 4. Ideogram of chromosome 3. The breakpoints of all patients with interstitial deletion 3p are illustrated: 1. Crispino et al., 1995: del (3p)(p11p14.1); 2. Sichong et al., 1981: del (3p)(p11p14.2); 3. Hertz et al., 1988: del (3p)(p11p14.2); 4. Neri et al., 1984: del (3p)(p12p14.2); 5. Naritomi et al., 1988: del (3p)(p12p14.2); 6. this report: del (3p)(p12p21.2); 7. Karimi-Nejad et al., 1990: del (3p)(p13p21.1); 8. Wyandt et al., 1980: del (3p)(p13.5p21.1); 9. Kogame & Kudo, 1979: del (3p)(p13p21); 10. Mitter et al., 1984: del (3p)(p13p21); 11. Short et al., 1986: del (3p)(p13.2p21).

TABLE I. Cytogenetic Findings and Major Phenotypic Abnormalities in Cases of Proximal Interstitial Deletion of 3p

	Crispino et al. [1995]	Sichong et al. [1981]	Hertz et al. [1988]	Neri et al. [1984]	Naritomi et al. [1988]	This report	Karimi-Nejad et al. [1990]	Wyandt et al. [1980]	Kogame and Kudo [1979]	Mitter et al. [1984]	Short et al. [1986]
Breakpoints in 3p	p11-p14.1	p11-p14.2	p11-p14.2	p12-p14.2	p12-p14.2	p12-p21.2	p13-p21.1	p13.5-p21.1	p13-p21	p13-p21	p13.2-p21
Typical facial phenotype	No photo	+	(+)	+	+	+	No photo	–	–	No photo	No photo
Ulnar deviation of hands	+	+	+	+	n.s.	+	+	n.s.	n.s.	n.s.	n.s.
Articular limitations	+	+	?	+	+	+	n.s.	+	n.s.	?	?
Foot deformities	n.s.[a]	+	n.s.	+	n.s.	+	+	+	+	n.s.	n.s.
Heart defect/ heart murmur	–	+	+	+	+	+	n.s.	–	–	+	+
Delayed psychomotor development	n.s.	+	? (fetus)	–	+	+	+	+	+	? (fetus)	? (fetus)
Intestinal malformation	n.s.	+	+	n.s.	n.s.	+	n.s.	+	n.s.	+	+
Coloboma of iris or retina[b]	n.s.	–	n.s.	n.s.	n.s.	+	n.s.	–	–	n.s.	n.s.
Heart defect	–	+	+	n.s.	+	+	n.s.	–	–	+	+
Atresia of the choanae	n.s.	n.s.	n.s.	n.s.	n.s.	+	n.s.	n.s.	n.s.	+	n.s.
Retardation of growth and development	–	+	?	+	+	+	+	+	+	?	?
Genital anomalies	n.s.	n.s.	n.s.	–	+	+	n.s.	+	n.s.	n.s.	n.s.
Ear abnormalities	+	+	+	+	+	+	+	–	+	+	n.s.

[a]n.s., not stated.
[b]The last six features are characteristic for CHARGE syndrome.

opment, (6) scrotal hypoplasia, micropenis, and abdominal testes, and (7) low-set and dysplastic but not protruding ears. None of the other reported patients with interstitial deletion 3p had signs of the CHARGE syndrome (Table I). The fetus reported by Mitter et al. [1984] was not described in detail; therefore the clinical diagnosis of CHARGE syndrome could neither be confirmed or refused.

CHARGE syndrome is a heterogenous entity. Most cases of CHARGE syndrome are sporadic, but there are familial observations [Pagon et al., 1981] and concordance in monozygotic twins [Oley et al., 1988] has been described, suggesting the possibility of a monogenic condition. In most of the published cases a chromosome abnormality was excluded, although some cases of CHARGE syndrome are combined with abnormal cytogenetic findings. Clementi et al. [1991] described two unrelated patients with CHARGE syndrome and an unbalanced translocation with monosomy of the terminal segment of 18q and a duplication of chromosome 2 (q37.3 → qter) in one patient and a monosomy of the segment p25.1 → pter of chromosome 3 and monosomy of the long arm of chromosome 22 in the other. Townes and White [1978] described a patient with CHARGE syndrome and a duplication 8q with other findings not described in this association. Shroff et al. [1981] described a boy with manifestations of CHARGE and deletion of 4q31, and Hurst et al. [1991] described a patient with a balanced translocation between the centromeric regions of chromosomes 6 and 8 and CHARGE syndrome. Emanuel et al. (1992) detected a microdeletion in the 22q11.2 region in one of 18 patients with CHARGE syndrome, and North et al. [1995] described a 4½-year-old girl with apparent CHARGE syndrome who had a de novo inverted duplication (14)(q22 → 24.3) and suggested that a locus for a gene causing some of the anomalies of CHARGE syndrome may reside in this chromosomal region. The combination of CHARGE syndrome with different chromosomal rearrangements makes it likely that it is a heterogenous disorder.

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